CHAPTER 11

General discussion

T. Verbeek
This thesis aimed to provide more knowledge of risk factors, long-term effects and treatment of anxiety and depression around pregnancy. We tested the following hypotheses:

1. Both the number of prior negative life events and aspects of low socio-economic status are positively associated with symptoms of anxiety and depression during pregnancy and with perinatal outcomes (chapter 3).
2. The associations of the number of prior negative life events with symptoms of anxiety and depression during pregnancy and with perinatal outcomes are negatively modified by aspects of socio-economic status (chapter 3).
3. In the Central American developing country Nicaragua, both the prevalence and the severity of anxiety and depression during pregnancy are higher than in developed countries (chapter 4).
4. Both symptom levels of anxiety and depression and personality traits are independently associated with meeting the World Health Organisation (WHO)-recommendation of six months exclusive breastfeeding; the latter association is mediated by symptoms of anxiety and depression (chapter 5).
5. Postnatal depression is associated with internalising and externalising mental health problems in the offspring during adolescence, independently of parental lifetime psychopathology (chapter 6).
6. Treatment of anxiety and depression during pregnancy using cognitive behavioural therapy leads to a stronger reduction in these symptoms (chapter 8) and more favourable perinatal outcomes (chapter 9), child development and child behaviour (chapter 10) as compared to care as usual.

After a summary of the main findings of this thesis follows a discussion of methodological issues that need to be considered before interpreting our findings. Finally, implications for clinical practice and recommendations for further research are provided.

Main findings

In chapter 2, screening and treatment of psychopathology during pregnancy in two women were described. The cases made clear how relevant early screening and treatment of symptoms of anxiety and depression are around pregnancy. Awareness and screening, followed by timely referral to a POP (psychiatry, obstetrics, and paediatrics)-team, may lead to more effective treatment, which may reduce or even prevent harmful consequences for all family members.

The first and second hypotheses were partly confirmed in chapter 3. Corresponding to present literature,46,47 we found that the number of
negative life events was positively associated with symptoms of anxiety and depression during pregnancy. This association increased in magnitude when the events happened more recently, except for the negative life events in the first 16 years of life (child traumas). These results were similar to those of studies among non-pregnant populations.\textsuperscript{49,50}

Furthermore, we found that maternal aspects of low socio-economic status (SES): low maternal educational level, maternal unemployment, and low family income were positively associated with symptoms of anxiety and depression during pregnancy. The associations of low SES with antenatal depression and anxiety have been shown earlier,\textsuperscript{46-48} although literature was conflicting about which aspects of SES play a role. Remarkably we did not see any association for educational level and employment status of the partner. Although maternal and paternal anxiety and depression frequently correlate,\textsuperscript{102} we did not find any literature on the association of paternal educational level and employment status on maternal anxiety or depression, but apparently these aspects of family SES have no impact on maternal psychopathology during pregnancy.

Associations of negative life events with adverse perinatal outcomes were observed in large population based studies (low birth weight: N=9,350, preterm birth: N=17,285).\textsuperscript{56,57} This also applied to the adverse effect of low SES on obstetric outcomes.\textsuperscript{58} In our study we found comparable trends, although not statistically significant, possibly due to the smaller sample size.

We found that the above-mentioned maternal aspects of low SES were not only positively associated with symptoms of anxiety and depression during pregnancy but that these also modified the effects of negative life events, significantly increasing them. When we repeated these analyses for perinatal outcomes, birth weight and gestational age, results showed similar trends, although they were mostly not statistically significant.

The third hypothesis was confirmed in \textbf{chapter 4}, wherein we presented that the prevalences of at least mild symptoms of anxiety and depression in our Nicaragua study were substantially higher than in our Dutch PAD-study. Furthermore, the severity of anxiety and depression, measured as mean symptom scores, were significantly higher in Nicaragua.

With respect to the burden imposed by mental disorders, mental health is known to be an under-researched health area, especially during pregnancy.\textsuperscript{116} Although the WHO recognises psychopathology as an important global health problem, which causes morbidity and mortality in both mother and child, the problem may be even bigger than earlier thought.\textsuperscript{14,59,60,93,104} Most earlier published prevalences of depression and/or anxiety during pregnancy were found in developed countries and were lower compared to those we found in our Nicaraguan sample, namely 10-15\%.\textsuperscript{2,47,105}
Literature demonstrating prevalences of antenatal anxiety and depression in developing countries outside Central America showed variable results.\textsuperscript{114,116-118} The prevalences of anxiety (41%) and depression (57%) in our sample of Nicaraguan pregnant women were comparable to these earlier studies in developing countries but notably higher than in developed countries.

A very small proportion of the women, less than ten percent, indicated that psychological help was available and that they knew how to reach that help. This statement was associated with higher anxiety scores but not with higher depression scores, suggesting that anxious women may know how to find psychological help.

In chapter 5, we partly confirmed our fourth hypothesis. We found associations of both the symptom levels of depression during and after pregnancy and the personality trait of openness with meeting the World Health Organisation (WHO) recommendation of six months exclusive breastfeeding. The latter was only partly explained by symptom levels of anxiety and depression. Therefore, mediation of this association may be largely caused by a direct effect of the openness personality trait on continuation of breastfeeding.

Earlier studies on the association of personality traits with breastfeeding initiation in the United States (n = 87)\textsuperscript{66} and with breastfeeding duration in the United Kingdom (n = 602)\textsuperscript{67,68} showed associations between high conscientiousness,\textsuperscript{67,68} high extraversion,\textsuperscript{66,67,68} low neuroticism,\textsuperscript{67,68} and high openness\textsuperscript{66} with breastfeeding. After adjustment for symptoms of anxiety and depression, we only found a significant association of high openness with reaching the WHO recommendation of providing six months exclusive breastfeeding. Our findings suggest that women who succeed in providing breast milk for six months might be more open to new experiences and appear to be more outgoing, seeking novelty and variety.

Furthermore, earlier studies on different subjects suggested that openness influences the processes of receiving information and decision-making. Individuals who showed high scores in openness found it easier to accept information and were more prone to choose the options for protection than people with other dominant personality traits.\textsuperscript{134,135} Thus, women with high levels of openness may accept information about breastfeeding more easily, and may be more likely to opt for protection of their infant than women with lower levels of openness. This may explain why women with higher scales of openness are more likely to meet the WHO recommendation.

Additionally, we found that personality traits were associated with anxiety and depressive symptoms around pregnancy. The latter findings are in line with earlier research conducted both in pregnant women\textsuperscript{71,72} and in the general population.\textsuperscript{69,70} However, earlier research was somewhat inconclusive about which trait is associated with psychopathology. In our
sample, low agreeableness, low conscientiousness, low extraversion, high neuroticism and high openness were associated with symptoms of both anxiety and depression during pregnancy and postpartum. In a recent meta-analysis the associations between personality traits of the five-factor model and risk of depressive symptoms were assessed in the general population.\textsuperscript{69} Our results correspond with theirs, suggesting that the associations between personality traits with both anxiety and depression symptoms are similar in the case of both pregnant and non-pregnant women.

Also the fifth hypothesis was partly confirmed. As described in chapter 6, we found that postnatal depression is associated with mental health problems in the offspring during adolescence. The relationship appeared to be specific for internalising problems because there was no association with externalising problems. Parental psychopathology did not fully explain this association, suggesting at least a partly direct psychological effect on the child postpartum.

Earlier studies have indicated that postpartum depression may increase the risk of emotional and behavioural problems in early childhood.\textsuperscript{29,33-37,150,153} However, there is debate whether negative effects of postpartum depression are lasting and extend into adolescence and what these effects are.\textsuperscript{37,40-44} A commonly recognised limitation was the absence of correction for parental lifetime history of psychopathology, thus leaving the possibility that the association is due to liability shared by mother and offspring.\textsuperscript{41} In our study we have overcome these limitations by correcting for dimension-specific parental loading for psychopathology. The observation that in our study the association between postpartum depression and internalising problems held up after adjustment for parental internalising psychopathology outside the postpartum period pleads for a direct psychological effect of postpartum depression. Such a direct psychological effect may be the result of impaired mother–child interaction, which has shown to lead to suboptimal attachment.\textsuperscript{29,47,150,152,153} Alternative explanations of the association of postpartum depression with mental health problems in the offspring include neglect or even abuse of the child\textsuperscript{172} or reduced frequency of breastfeeding.\textsuperscript{173}

The sixth hypothesis was threefold, corresponding to three chapters relating to the randomised controlled trial we performed as described in chapter 7.

In chapter 8, we showed no significant differences between the group of women who received cognitive behavioural therapy, and the group of women who received care as usual. Thus, we could not confirm that cognitive behavioural therapy leads to a stronger reduction of anxiety and depressive symptoms at 36 weeks of gestation, as compared to care as usual.

Our results are somewhat surprising because there is strong evidence that cognitive behavioural therapy is effective in treating anxiety and depressive symptoms outside pregnancy.\textsuperscript{47,59} However, recent studies presented that the
efficacy of both psychotherapy and pharmacotherapy may have been overestimated.\textsuperscript{247,248} Our results are consistent with an earlier study on 277 women with anxiety and depressive symptoms/disorders wherein no beneficial effects of cognitive behavioural therapy were demonstrated.\textsuperscript{82} Conversely, another study showed a significant decrease in antenatal depression symptom levels due to cognitive behavioural therapy among a sample of 217 Latina women with subclinical symptoms.\textsuperscript{81} Finally, a small pilot study including 36 pregnant women with a depressive disorder compared a home-based cognitive behavioural therapy intervention with care as usual and also found a reduction in depression symptom levels in the therapy group, although not statistically significant.\textsuperscript{80}

A major consideration in this trial is the observation that the mean levels of anxiety and depression symptoms were relatively low at screening. A substantial percentage of the women (127 of the 282; 45\%) had subclinical symptoms, indicating that there may have been less room for improvement, i.e. further decline of symptom levels. Nevertheless, when assessing women with clinical symptoms only, no beneficial effects of cognitive behavioural therapy were demonstrated either. Unexpectedly, anxiety and depression symptom levels were increased in the group receiving cognitive behavioural therapy relative to the women who received care as usual, although this difference was not statistically significant.

Additionally, as studied in \textbf{chapter 9}, we observed no differences in both birth weight and gestational age between both groups overall. However, in participants with a present DSM-IV anxiety diagnosis, we found that the mean birth weight was over 275 grams lower and the mean gestational age approximately a week lower in the cognitive behavioural therapy group, as compared to care as usual. Our per-protocol analyses, wherein perinatal outcomes of women who received at least six CBT sessions were compared with women who received CAU, demonstrated an even stronger association. These adverse effects could not be explained by use of antidepressants or benzodiazepines, higher proportions of induced labour or caesarean section, smoking, or symptom levels of depression, but may partly be explained by the anxiety symptom level during pregnancy, which was increased in the group receiving cognitive behavioural therapy relative to the women who received CAU.

Although scarcely studied, very limited literature suggests that cognitive behavioural therapy may have adverse (side) effects.\textsuperscript{242} Providing cognitive behavioural therapy for anxiety symptoms on the one hand treats symptoms, but on the other hand confirms that there are symptoms and the (expected) exposure increases anxiety in the short term, that these are disadvantageous, and that these should be treated.\textsuperscript{243} The latter thoughts may increase anxiety symptoms, instead of decreasing them. As mentioned earlier, our mediation analysis shows that the difference in birth weight between both groups is
partly mediated by anxiety symptom levels at 24 weeks of pregnancy. In our CBT treatment, this is the moment when women receive their first sessions.

Consequently, we propose that the demonstrated adverse effects may be due to increased stress levels, conceivably induced by the provided CBT. Indeed, the dialogues and exposure during the sessions in CBT may be confrontational and may induce stress in the short-term, instead of reducing stress levels. Our per-protocol analyses demonstrated even stronger adverse effects, suggesting an exposure-response mechanism: the more CBT sessions the women received, the worse the perinatal outcomes.

Finally, in chapter 10, our preliminary results (child behaviour N=168, child development N=175) show no differences in behavioural and developmental problems or cognitive, fine and gross motor development in the offspring at 18 months of age.

A recent Pakistani randomised controlled trial showed no effect of antenatal cognitive behaviour therapy on offspring cognitive, socio-emotional, or physical development at age 7. However, this study only assessed parent-reported child development and did not investigate effects on offspring behavioural problems. Nevertheless, our study extends this conclusion to both behavioural and emotional problems as well as the child's cognitive, fine and gross motor development, as measured by trained research assistants using the widely known Bayley Scales of Infant and Toddler Development, Third Edition.

Methodological considerations

The research presented in this thesis focuses on quantifying associations between exposure to risk factor(s) or treatment and clinical outcomes. In every clinical epidemiological study, interpretation of associations should be preceded by an evaluation of potential bias. Three types of bias should be distinguished: information bias, selection bias, and confounding. The next paragraphs will discuss an evaluation of the potential of these types of bias, as well as the precision of our findings.

Information bias

One of the considerations regarding this thesis is the use of questionnaires, which have been used in almost all analyses. These questionnaires come with their typical limitations, i.e. misclassification and the potential for information bias.

For example, in chapter 3, negative life events were documented using retrospective self-report checklists, which may have been prone to recall bias through its potential link with symptoms of anxiety and depression at the
time of the assessments. Indeed, when people are anxious or depressed, they may think about adverse life experiences more often than people without symptoms of anxiety or depression. Additionally, in chapter 6, recall bias may have played a role in identifying cases of postpartum depression. Nevertheless, as mentioned earlier, retrospectively assessed adverse experiences, such as postpartum depression, do involve false negatives but rarely involve false positives. Thus, in our study it is quite likely that those women who did report a postpartum depression actually had suffered a postpartum depression while an unknown number of women who actually suffered a postpartum depression did not report it. Consequently, the association between maternal postpartum depression and psychopathology may have been diluted by non-differential determinant misclassification, i.e. recall of postpartum depression was assumed to be independent of the presence of the adolescents’ mental health problems. Therefore, the real association may be stronger than we observed. In chapter 5, we assessed exclusive breastfeeding at six months postpartum, as recommended by the WHO. It is not inconceivable that women give socially desirable answers, i.e. to answer positively to this question while they actually did not provide exclusive breastfeeding for six months. For this reason, it may be expected that the neuroticism personality trait, which is a trait characterised by anxiety and vulnerability, was a priori more likely to be associated with the WHO recommendation. Conversely, in our sample the openness to experience personality trait was associated with six months exclusive breastfeeding. A so-called self-serving bias was therefore less likely to have occurred.

Throughout the thesis, symptom levels of anxiety and depression were measured using widely recognised questionnaires. The Spielberger State Trait Anxiety Inventory (STAI) was used to assess symptom levels of anxiety. In each analysis, we used the 6-item short-form to measure anxiety symptom levels which produces scores similar to those obtained using the full-form. The cut-off score for an at least moderate level of anxiety is >42. This commonly used questionnaire has a good internal consistency (average Cronbach’s alpha of .89). The 10-item Edinburgh Postnatal Depression Scale (EPDS) was used to measure depression symptom levels. The cut-off score for an at least moderate level of depression is ≥12. The 10-item EPDS has shown good internal validity with a Cronbach’s Alpha of 0.82. A limitation is that both are self-report questionnaires and only measure symptom levels, so no diagnosis could be made. On the other hand, assessments of symptom levels are able to show smaller changes and thus may be more precise. Additionally, in Part II, we performed the widely validated Structured Clinical Interview for DSM-VI Disorders (SCID-II) to assess the presence of an anxiety and/or depressive disorder according to the DSM-IV.
In the Nicaragua study, we were not able to perform a SCID interview, thus in chapter 4 our analyses were limited to data from questionnaires. Even though the STAI and EPDS are commonly used worldwide, misunderstandings of the questionnaires, possibly due to illiteracy, may have led to over- or underreporting. As demonstrated in earlier research, a lower educational level is associated with a higher rate of psychopathology during pregnancy. Nevertheless, when a participating woman was illiterate, we read the questionnaire aloud. We believed this was a better method then excluding all illiterate women. Additionally, our analyses showed similar results in both illiterate and literate women. Furthermore, cut-off values for both STAI and EPDS questionnaires may depend on different cultural backgrounds. However, since this is the first study among Nicaraguan women, we considered it justified to use the widely recognised cut-off values for an at least moderate level of anxiety and depression, as mentioned above.

As mentioned in chapter 6, the parental loadings for psychopathology used in the analyses in that chapter were rough approximations of genetic loading, since these measurements necessarily include (shared) environmental risk for decreased mental health as well. Methodologically, it would be more refined to report distinct effects of both genetic loading and environmental risk factors. However, research showed that the genetic basis for the intergenerational transmission of depression is not (yet) identified and that shared environmental risk factors make important contributions to most forms of child and adolescence psychopathology. Thus, currently it is impossible to measure separate effects of genetic loading and environmental effects. Nevertheless, the results of the analyses showed that the association of postpartum depression with internalising mental health problems remained statistically significant after correction for parental loading for lifetime internalising mental health problems. Thus, independent of both genetic loading and (shared) environmental risk for decreased mental health, postpartum depression has shown to have an adverse effect on the offspring, even in adolescence.

The most important finding in chapter 9 is, apart from the absence of an advantageous overall effect, the adverse effect of cognitive behavioural therapy on both birth weight and gestational age in participants with a present DSM-IV anxiety diagnosis. Post-hoc exploratory mediation analyses showed that this adverse effect on birth weight but not on gestational age was partly (22.6%) mediated by anxiety symptoms at 24 weeks of gestational age. In our treatment, this was the moment when women received their first therapy sessions. Consequently, we propose that the demonstrated adverse effects may be due to increased stress levels, conceivably induced by the provided cognitive behavioural therapy. Indeed, the dialogs and exposure sessions, using imagery and re scripting, may be confrontational and may induce stress at short-term, instead of reducing stress levels. Our per-protocol analyses, wherein perinatal outcomes of women who received at least six therapy sessions were compared with women who received care as
usual, demonstrated even stronger adverse effects, suggesting an exposure-response mechanism: the more therapy sessions the women received, the worse the perinatal outcomes. An important limitation in this chapter is that we did not measure any biological stress markers during pregnancy. An increase in physiological stress measures, such as cortisol levels, (nor)adrenal hormones or other biological parameters could have provided us with more information about the mediators of the observed effects.

In chapter 10, we assessed effects of antenatal cognitive behavioural therapy for anxiety and depression on offspring behaviour problems and development at age 18 months, compared to care as usual. We showed small but not statistically significant effects of cognitive behavioural therapy on child behaviour problems and cognitive, fine motor and gross motor development, as compared to care as usual.

Behavioural and developmental problems were assessed using the Child Behaviour Check List for children of age 1.5 to 5 (CBCL 1.5–5) including the Caregiver-Teacher Report form (C-TRF). This well established, reliable and valid scale comprises seven syndrome scales: emotionally reactive, anxious depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive problems. In addition, it contains scales for internalising, externalising and total problems. Symptom scores may further be related to formal DSM-diagnostic criteria. The CBCL 1.5-5 is considered a sensitive instrument also deployed in several earlier studies. For the assessment of psychopathology in preschool children it is considered essential to obtain information from different sources. Therefore we decided to include the C-TRF for both the parents and the caregivers of the children other than their parents. Parents were instructed to hand these lists to the actual other caregivers of their children, e.g. grandparents, babysitters, kindergarten-coaches, etc. This methodology was intended to minimise misclassification and information bias.

Cognitive, fine and gross motor development levels were assessed using the Bayley III Scales of Infant and Toddler Development (BSID-III). It was individually administered and consisted of three subscales: cognitive development (mental development index), gross and fine motor development. This tool is widely used in both research and clinical settings and is considered the best and most applied method for the assessment of the child’s development to date. Importantly, the instrument has shown to be sensitive. In the context of our study, maternal anxiety in pregnancy explained as much as 11% of the variance in the Bayley scores in a study among two-year-old toddlers. All participating women received invitations for the BSID-III when their offspring were aged 18 months. Tests were performed in hospitals or at participant’s homes. Trained research assistants masked to study group provided the cognitive and motor scales. Interobserver variance was limited by providing supervision after reviewing and reassessing videotaped BSID-III assessments.
Selection bias

Some of the potential limitations of practically every population-based study are the risks of selective recruitment by researchers or healthcare providers and self-selection bias due, for example to low willingness to participate in the study. The strategies to handle this risk differed between the cohorts.

In the main TRAILS cohort, as described in chapter 6, there was no selective recruitment at personal level, because recruitment involved municipalities, which provided names and addressed of all eligible inhabitants. Because the recruitment of participants in the TRAILS-CC cohort involved all children who have been referred at least once to the child psychiatric outpatient clinic of the University Medical Center Groningen at any point in their life, there was no selective recruitment either. Selection bias due to willingness of participation was assessed by testing differences between responders and non-responders. Teacher-rated problem behaviour and socio-demographic variables were used in the TRAILS cohort\textsuperscript{159} and psychopathology subscales, language performance, and demographic variables in the TRAILS-CC cohort\textsuperscript{158}. There were no significant differences between responders and non-responders, suggesting that a selection bias was unlikely\textsuperscript{159}.\textsuperscript{158}

In the Nicaraguan cohort, as described in chapter 4, we invited all women visiting one of the participating community health centres or the participating hospital for regular pregnancy consultations or in the final phase of pregnancy. Of the 105 eligible women, 98 (93\%) women were willing to participate. This high participation rate decreases the possibility of a noticeable selection bias.

In the Pregnancy Anxiety and Depression (PAD)-study, as studied in chapters 3-5, all pregnant women in their first trimester of pregnancy visiting a total of 109 collaborating primary obstetric care centres and 9 hospitals in the Netherlands were invited to participate. It should be noted as a limitation that, due to logistical reasons, it has been impossible to determine how many women have actually been invited and consequently to determine the exact participation rate. Because the number of participating women was considerably lower than expected we conducted a survey among participating midwives and gynaecologists\textsuperscript{252}. The results indicated that time constraints were mostly deemed responsible and that they had not specifically invited women they suspected to have risk factors, psychopathology or other conditions. Therefore, we have no reason to believe that responders and non-responders differed in any considerable way with respect to characteristics relevant to the present study. In other words, we do not believe that there was a relevant selection bias.
A potential limitation of PROMISES-study as described in the chapters in Part II of this thesis is the low participation rate of women who were invited to participate in the trial. Only 282 (28%) of the 1007 eligible women agreed to participate in our randomised controlled trial. Our response rate was somewhat low when compared to that of other similar studies that included pregnant women who were not active help-seekers. The study of Austin et al., that included pregnant women with subclinical symptoms or anxiety and depressive disorders, showed a slightly higher response rate of 39%. The randomised controlled trial by Le et al., that included women with subclinical symptoms or a previous depression had an even higher response rate of 70%. In our study, of the 239 women who declared the reason of non-participation in the trial, 160 (67%) were not interested in participating in a trial: they wanted to either have or have not therapy, but did not want to be randomised. Twenty-eight (12%) women addressed practical issues, e.g. they expected to have no time for therapy sessions, had to care for other children or had to work. The remaining 51 (21%) did not acknowledge their symptoms and/or felt no need for therapy. A selection bias due to low willingness to participate in this trial may have occurred, possibly an explanation of the low symptom levels of the participants, compared to earlier studies. After randomisation, an additional total of 15 women who were randomised to the group that would receive cognitive behavioural therapy, eventually refused therapy. Although literature states that women seem to have a preference for psychological therapy over antidepressants, our figures suggest that at least a proportion of these women do not want cognitive behavioural therapy.

Confounding

Confounding is a type of bias which may occur in observational research. A confounding variable is linked to both the presumed determinant and the outcome and may interrupt a causal relation. By adding possible confounders to a regression analysis, it is possible to correct for confounding, leading to more valid results. Resulting from the nature of an observational study, correction for confounding is only possible for known variables.

For example, in chapter 4, we evaluated the differences in anxiety symptom level scores between Nicaragua and the Netherlands. The scores were remarkably higher in Nicaragua and while one of the possible differences between the two cohorts is that in the developing country of Nicaragua women experience more negative life events than women in the Netherlands. However, the low SES of Nicaraguan women compared to Dutch women may be the underlying cause of their symptomatology. Low socio-economic status may lead to both negative life events and psychopathology. Another possibility is that low SES may lead to negative life events, which may increase the risk of psychopathology. The first can be assessed by adding SES as independent variable to the regression analysis between negative life events and psychopathology. The latter can be assessed using a mediation
Unfortunately, this study was only an explorative study and did not assess possible explanations for the high symptom level scores, such as negative life events.

As discussed in chapter 1, earlier research in the association between antenatal psychopathology and adverse effects in the offspring may be causal or non-causal. Causal effects may be divided into direct, e.g. foetal programming, and indirect, e.g. more smoking and less breastfeeding. A non-causal explanation may be a shared genetic or environmental predisposition by mother and child. Because all earlier research on this topic is observational, this confounding bias by genetics or environment could not be excluded. In our research in Part II of this thesis, we aimed on overcoming this bias by performing a randomised controlled trial wherein we attempted to lower the anxiety and/or depression symptom levels in one group and compare outcomes to the other group. In the event of observing positive effects on symptom levels, i.e. lower levels in the cognitive behaviour therapy group when compared to the care as usual group (positive maternal effects), and of observing positive effects on perinatal, behaviour and/or cognitive (offspring) outcomes, we should have concluded that a causal explanation was more likely. In contrast, in the event of observing positive maternal effects but no offspring outcomes, a causal explanation was less likely. Unfortunately, no effects on maternal symptom levels were observed, thus we are not able to draw any conclusion on the causality issue.

**Precision**

Precision stands for the extent wherein results will be similar when the research is repeated, or in other words: the measurement of noise, and is inversely related to random error. In general: the greater the sample size, the smaller the noise, and the greater the precision. In all chapters, we considered p<0.05 as statistically significant, and we reported the corresponding 95% confidence intervals as well.

One issue relating to precision concerns the results of chapter 9. This chapter provides evidence for an adverse effect of CBT on perinatal outcomes when provided to pregnant women with a DSM-IV anxiety diagnosis. However, this is a subgroup analysis and not a trial wherein solely women with an anxiety diagnosis were included. Nevertheless, we believe that this study gives a strong indication that cognitive behavioural therapy has a possible adverse effect on the unborn child and therefore should not be provided to pregnant women with a DSM-IV anxiety diagnosis. Ideally, further research will be conducted on antenatal treatment options in women with anxiety disorders, wherein perinatal outcomes should be studied.
Implications for clinical practice and future research

The findings in this thesis add to the knowledge of risk factors, long-term effects and treatment of anxiety and depression during and after pregnancy. Overall, the findings in this thesis provide several implications for both (future) clinical practice and research.

Identification of personal characteristics

Modern health care is evolving; in history, medical practice was based on doctors’ personal experience and opinion. This way of performing medicine is largely substituted by evidence-based medicine. In vitro studies, animal models, epidemiological studies and trials led to uniform diagnostic, prognostic and treatment guidelines. A limitation herein is that less attention may be paid to personal differences between patients. Indeed, due to limited resources, studies are performed on groups of patients, which are heterogeneous by definition because of participants’ different individual characteristics. In the future, this ‘group-based evidence’ may be replaced by a more personalised medicine: taking the personal characteristics of the individual patient into account, healthcare providers may perform personalised medicine. Parts of this thesis may contribute to this way of providing this personalised healthcare.

As discussed in chapter 2, treatment of psychopathology in pregnant women may be complex and severe cases should be performed by a POP (psychiatry, obstetrics, paediatrics)-team. However, the general practitioner and the midwife should have a major role in screening of anxiety and depression in pregnant women. General practitioners mostly have a long-term relationship with their patients and know them well and therefore are acquainted with their patient’s family history, socio-economic status (SES), major (negative) life events, as well as medical (psychiatric) history.

As summarised above, in chapter 3, both a low SES and a high number of negative life events may have an adverse effect on symptomatology of anxiety and depression during pregnancy. An implication of the findings may be that more attention should be paid to the assessments of both negative life events and earlier mentioned aspects of SES in designing and implementing psychosocial interventions for pregnant women. Interventions are presumably most cost-effective when targeted at women with a low SES and with a history of multiple life events, in particular those who have experienced child traumas or recent events, because in that group the greatest advantage may be gained.

In chapter 5, we studied personality traits, symptoms of anxiety and depression and its association with exclusive breastfeeding, which has well-known health benefits for both mother and child. Our analyses show an
association of both the openness personality trait and symptoms of depression during pregnancy with exclusive breastfeeding for six months, as recommended by the WHO. The resulting advice to midwives, general practitioners and other maternal healthcare providers should be both to screen for symptoms of depression and to determine the personality traits of all pregnant women.

In the contemporary daily practice, it is uncommon to assess personal features as number of negative life events, SES, or personality. Additionally, in study settings personality is mostly assessed using questionnaires but this is highly unusual in clinical practice. Therefore, unless personality traits are assessed using shorter screeners, it is unlikely that this study will imply that above-mentioned maternal healthcare providers will integrate such questionnaires into their daily practice. Nevertheless, these chapters add to our understanding of interpersonal differences in the risk of anxiety and depression during pregnancy and in the chance of fulfilling the WHO breastfeeding recommendation. Furthermore, when personalised evidence-based medicine will become more common, the results as described in this chapter may help healthcare providers to decide which of their patients may need extra attention to fulfil the recommended breastfeeding results. In the future, new technological innovations may support screening in medical practice. For example, using online platforms, risk stratification may become easier, more reliable and less time-consuming during the consultation.

_Antenatal psychopathology in Central America_

The results of chapter 4, as summarised above, strongly suggest the need for further research. Compared to developed countries, lower education, lower income, younger maternal age, and more negative or traumatic life events could be factors in the Central American country Nicaragua that relate to a higher risk of suffering from psychopathology during pregnancy.46-59

The WHO reported that in Nicaragua only 1% of the total health care budget is reserved for mental health, and 91% of that is given to psychiatric hospitals.106 Under these circumstances, it is likely that relatively mild mental health issues in a specific population such as pregnant women are neglected. Psychological help may not be commonly available for the women in the rural areas, therefore in addition to more knowledge about the problems, the possibilities of providing effective treatment if needed, e.g. psychotherapy for antenatal psychopathology, should be explored. It would be desirable to investigate the results of this possible solution in a follow-up study in the same geographical area.
Effects of postpartum depression on offspring

In chapter 6, we demonstrated that postnatal depression is associated with internalising but not with externalising mental health problems in the offspring during adolescence and that this association is only partially explained by parental lifetime psychopathology. Therefore, mediation of this association may be largely caused by a direct psychological effect on the child in the postpartum period, e.g. as a result of impaired mother–child attachment. Early screening for and treatment of maternal postpartum depression may decrease her depressive symptoms\textsuperscript{175-177} and, if the association appears causal, may thereby prevent internalising psychopathology in the offspring, ultimately in adolescence.\textsuperscript{178} In addition, because particularly early management of psychopathology in adolescence may reduce symptoms,\textsuperscript{179,180} the offspring of mothers with a history of postpartum depression could be monitored more closely for internalising problems in early adolescence.

Treatment of antenatal psychopathology using cognitive behavioural therapy

In part II of this thesis, the effects of cognitive behavioural therapy for anxiety and depression during pregnancy were assessed. In contrast of what is suggested by current international guidelines,\textsuperscript{73-76} this thesis demonstrates no advantageous effect on maternal symptom level during pregnancy (chapter 8), perinatal outcomes (chapter 9), behavioural and emotional problems or the child’s development (chapter 10).

The results of chapter 8 imply that other interventions than cognitive behavioural therapy should be studied. Patient engagement seems to be a predictor of greater reductions in interventions on both anxiety and depressive symptoms.\textsuperscript{226} Thorough explanation of the sense of therapy, leading to increase of motivation, but not to increase stress, may be helpful. Additionally, less intensive interventions, e.g. relaxation therapy, support, and internet-based interventions, combined with screening tools to acknowledge undesirable increases in anxiety, depression or stress levels should be explored as therapy for subclinical symptoms.

Furthermore, chapter 9 showed that cognitive behavioural therapy may not only have no positive effects on major perinatal outcomes, but in fact may have an adverse effect, when provided as early treatment in pregnant women with a DSM-IV anxiety diagnosis. Additionally, in pregnant women with a DSM-IV depression diagnosis, or without any DSM-IV diagnosis, no positive effects on perinatal outcomes were observed. Therefore, although antenatal cognitive behavioural therapy is most likely to be effective for prevention of postpartum depression, this therapy should not be provided as prevention of low birth weight or prematurity in women and should be reconsidered as
antenatal treatment of anxiety symptoms in the light of possible long-term adverse effects of both low birth weight and low gestational age.253

Our daily medical practice is as much as possible founded on research (evidence-based medicine), wherein a meta-analysis of multiple randomised controlled trials is considered as the highest level of evidence. However, due to ethical concerns on performing research on pregnant women, to date the effectivity of anxiolytics and antidepressants during pregnancy has not been evaluated. The results of our trial in Part II of this chapter provides evidence for an adverse effect of CBT on perinatal outcomes when provided to pregnant women with a DSM-IV anxiety diagnosis. However, this is a subgroup analysis and not a trial wherein only women with an anxiety diagnosis were included. Nevertheless, we believe that this study gives a strong indication that cognitive behavioural therapy has an adverse effect on the unborn child and therefore should not be provided to pregnant women with a DSM-IV anxiety diagnosis. Preferably, further research will be conducted on antenatal treatment options in women with anxiety disorders, wherein perinatal outcomes should be studied. Additionally, future studies could explore potential underlying biological mechanisms and possible long-term effects of cognitive behavioural therapy during pregnancy on the offspring, which in chapter 10 of this thesis have not been demonstrated. Nevertheless, ethical concerns in performing a trial using a possibly harmful treatment in pregnant women should be taken into account.

Earlier research in general population settings showed cognitive behavioural therapy to have unremitting positive effects in treating anxiety and depression.46,59 In the light of both this research and the findings in this thesis, it may be recommended that women of fertile age should be screened for (risk factors of) anxiety and depression and, when desired, treated using cognitive behavioural therapy before, but not during pregnancy.

Conclusion

Psychopathology during and after pregnancy is an important personal and public health problem with adverse consequences for mother and child in both the short term (e.g. lower probability to exclusively breastfeed for six months) and the long term (e.g. higher change of offspring mental health problems during adolescence). In Central America, anxiety and depression during pregnancy is highly prevalent and symptom levels are more severe than in developed countries. Low-income women who recently or as a child experienced negative life events are more likely to develop symptoms of anxiety and depression. Conversely, cognitive behaviour therapy as a treatment for subclinical psychopathology should not be provided during pregnancy because of the absence of positive maternal and child developmental effects and the presence of possible adverse effects on perinatal outcomes.